(February 4, 1975)

REVIEW BY CORN REFINERS ASSOCIATION, INC.
of

SCIENTIFIC LITERATURE REVIEW ON GENERALLY REGARDED AS SAFE (GRAS) FOOD INGREDIENTS -

CORN SUGAR

PB-223 853

CORN REFINERS ASSOCIATION, INC.
1001 CONNECTICUT AVENUE, N. W. WASHINGTON, D. C. 20036

ROBERT C. LIEBENOW
PRESIDENT

February 4, 1975

Select Committee on GRAS Substances
Federation of American Societies for
Experimental Biology
9650 Rockville Pike
Bethesda, Maryland 20014

Gentlemen:

The Corn Refiners Association, Inc., represents 11 of the 12 companies in the United States engaged in the wet milling of corn to produce starches, corn syrup, dextrose, corn oil, and other products. This industry manufactures most of the dextrose produced and used in the United States, and, consequently, is an interested party in connection with the Scientific Literature Reviews on GRAS Food Ingredients - Corn Sugar. A technical committee from our industry, with members having experience and training on this subject, has reviewed this document and prepared comments and suggestions concerning this material which are pertinent to the FASEB review.

The Federal Register, Vol. 38, No. 143--Thursday, July 26, 1973, (pages 20053 and 20054) signed by the Commissioner of Food and Drugs, provides the mechanism and urges interested parties to comment on the Scientific Literature reviews. The Corn Refiners Association, Inc., is pleased to submit its comments as provided in that document.

Accordingly, we are providing the requested 10 copies for FASEB and the original and two copies to the Bureau of Foods of the Food and Drug Administration as requested by the Commissioner.

We trust that this information will be of value in assisting the FASEB Committee in reaching an appropriate conclusion on this matter.

Sincerely,

Robert C. Liebenow
President

RCL:jm

Attachments

REVIEW BY CORN REFINERS ASSOCIATION, INC.

(February 4, 1975)

of

SCIENTIFIC LITERATURE REVIEW ON GENERALLY RECOGNIZED AS SAFE (GRAS) FOOD INGREDIENTS - CORN SUGAR

Prepared for Food and Drug Administration
by Food and Drug Research Laboratories,
Incorporated (1973) Document PB-223 853

FINAL REPORT

of the

CORN REFINERS ASSOCIATION, INC.

on

CORN SUGAR (PB-223 853)

In mid-1974, the Corn Refiners Association, Inc. appointed a committee to review the document, "Scientific Literature Reviews on Generally Regarded as Safe (GRAS) Food Ingredients - Corn Sugar", PB-223 853. This committee included scientists with training and experience in chemistry, biochemistry, nutrition and food technology. All committee members are employed by member companies of the Association. Following completion of this study by the committee, its report was circulated to all member companies for further review. The following final report constitutes the comments and recommendations of the Corn Refiners Association, Inc., and its member companies.

I. GENERAL COMMENTS

Unfortunately, the title selected for this GRAS Literature Review was "Corn Sugar". This is a nonspecific, undefinable term that is almost meaningless in modern technical literature. Previous to the mid-1920's, any solidified starch hydrolysate, rich in dextrose, was referred to as "corn sugar". With the development of the crystalline dextrose process of Newkirk in the mid-1920's, crystalline alpha-d-glucose monohydrate became available and this crystalline sugar was offered to the American food processor as dextrose. As production facilities expanded for crystalline dextrose, it has become the prevalent sugar produced by hydrolysis of corn starch and the so-called "corn sugars" have gradually disappeared from the market.

Three Corn Refiners Association, Inc. members are principal producers of dextrose in the United States (Clinton Corn Processing Company, CPC International Inc., and A. E. Staley Manufacturing Company).[1/]

1/ The 1974-1975 OPD Chemical Buyers Directory, published by Chemical Marketing Reporter, lists, in addition to these companies, the following suppliers of dextrose, anhydrous and/or dextrose, hydrous (hydrate): J. T. Baker Chemical Co., Conroy Products Co., Mallinckrodt Chemical Works, S. B. Penick & Co., Pfanstiehl Laboratories, Inc., Ruger Chemical Co., Inc., & White Cross Laboratories, Inc.

Because only crystalline alpha-d-glucose (monohydrate or anhydrous), or solutions thereof, are currently sold as food ingredients, the monograph should have been limited to information and data gained on this -- and only this -- identifiable sugar. Dextrose is now specifically defined in the Codex Alimentarius Commission* Standards (CAC/RS 7-1969 and CAC/RS 8-1969) and in Food and Drug Administration Rules and Regulations [Title 21, Subchapter B, Part 26, Nutritive Sweeteners - see Attachment 1.]

All of the dextrose produced in the United States uses food grade starch as the raw material. The process involves acid or enzyme liquefaction of the starch followed by saccharification with glucoamylase. Small quantities of fat are removed from the hydrolysate by mechanical processes. Color, flavor, proteins and salts are removed by treating the hydrolysates with activated carbon and ion-exchange deionization. The resulting nearly water-white solutions are concentrated and crystallized. The crystalline alpha-d-glucose monohydrate is removed by centrifugation, dried and shipped as dextrose. If dextrose hydrate is dissolved and recrystallized at elevated temperatures, anhydrous dextrose is produced.

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* Joint Food and Agriculture Organization of the United Nations/World Health Organization Food Standards Programme, Codex Alimentarius Commission.

Dextrose is a highly purified, white crystalline product commercially available throughout most of the world. It is also sold commercially as an aqueous solution prepared by redissolving crystalline dextrose in water. When so dissolved in water, an equilibrium mixture of the alpha and beta forms result.

Dextrose is widely used in foods such as yeast-raised goods, canned fruit, pickles, candy, fruit drinks, carbonated beverages, bakery sweet goods, dry mixes of all types, chewing gum and many other miscellaneous food products. The principal properties utilized are:

1. An easily assimilated source of nutritive carbohydrates
2. Easy fermentability
3. Mild sweetness
4. Stability toward acid hydrolysis
5. High osmotic pressure
6. Moderate humectancy
7. Easy caramelization to produce desirable flavors, colors and odors
8. Preservative
9. Other miscellaneous properties.

Dextrose solutions are commonly used for intravenous feeding. A special USP Grade of anhydrous dextrose is used for this purpose. USP Grade is not used in food products. Approximately 10 million pounds of USP dextrose are used per year in the United States.

The average production of dextrose in the United States for the years of 1970 through 1973 was 1,263 million pounds per year. By far the major portion of this dextrose was used for human food. Appreciable quantities are used as a raw material by the pharmaceutical industry for the production of citric acid, sorbitol, ascorbic acid, antibiotics, etc. During the years 1970 through 1973, approximately 14% of the dextrose produced in the United States was sold to the pharmaceutical industry.

Large quantities of dextrose are also produced and used throughout the rest of the world.

II. COMMENTS ON BIBLIOGRAPHY

The Scientific Literature Review - Corn Sugar, prepared by Informatics, Inc., is complicated by the inclusion of hundreds of references in the bibliography that do not

pertain to the subject. The volume of irrelevant references makes a thorough, meaningful review most difficult. We believe that all references specifically concerned with fructose, sucrose and other sugars and not to dextrose should be deleted as irrelevant. Only experimental data concerned with dextrose and/or its comparison to other carbohydrates should be included as relevant material.

Further, all analytical data, properties, specifications, etc., relating to fructose and sucrose should be deleted.

III. COMMENTS ON OPINIONS EXPRESSED BY INFORMATICS, INC.

We recommend that all interpretations based on opinions of the reviewer should be deleted. For example, most of the material on page 3 is irrelevant to the safety of dextrose and simply states the opinion of the reviewer. It shows a strong prejudicial attitude on the part of the Informatics, Inc. reviewer. Other evidences of this attitude show at other points in the literature review.

IV. CHEMICAL INFORMATION

(Listing below replaces the information on pages 4, 5 & 6 of Informatics, Inc. report.)

A. Nomenclature

1. Common Names

(a) Dextrose
(b) Alpha-d-glucose

2. Chemical Names

(a) Alpha-d-glucopyranose

3. Trade Names

(a) Cerelose
(b) Clintose
(c) Staleydex

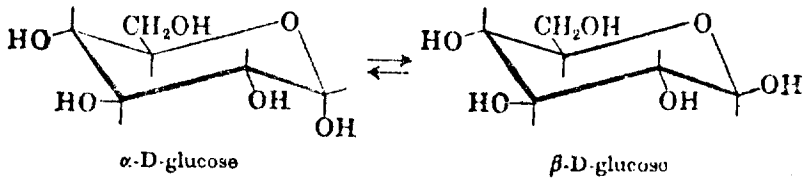
4. Chemical Abstracts Registry Number

Dextrose - 000050-99-7

B. Empirical Formulas

$C_6H_{12}O_6$ and $C_6H_{12}O_6H_2O$

C. Structural Formula



α-D-glucose β-D-glucose

At equilibrium a solution of glucose contains 36% beta-D-glucose.

D. Molecular Weight

Dextrose anhydrous - 180.16
Dextrose monohydrate - 198.18

E. Specifications

See 21 CFR 26.1, 26.2

F. Description

1. General Characteristics

Dextrose is a white, crystalline, mildly sweet solid

2. Physical Properties

Alpha-form (anhydrous)
- crystallizes from hot ethanol or water
- melting point 146 degrees C.
- specific optical rotation + 52.5 to 53.0 degrees
- pH of 0.5 molar aqueous solutions 5.5 to 6.5

Density of water solutions of dextrose

Concentration by weight in vacuo	Density 20°/4° observed
Percent	
6.5	1.02361
12.5	1.04799
18.5	1.07329
23.5	1.09524
28.9	1.11963

n_D^{20} 10% solution 1.3475

One gram dissolves in 1.1 ml water at 25 degrees; in 0.8 ml at 30 degrees; in 0.41 ml at 50 degrees; in 0.28 ml at 70 degrees; in 0.18 ml at 90 degrees; in 120 ml of methanol at 20 degrees. Very sparingly soluble in absolute alcohol, ether, and acetone; soluble in hot glacial acetic acid, pyridine, and aniline.

3. Stability

(a) Dextrose monohydrate

Stable for long periods at room temperature. Shipped in 100# multi-wall paper bags, bulk rail hopper cars and bulk motor trucks.

(b) Dextrose anhydrous

Shipped in 100# multiwall paper bags. Keeps for long periods of time when stored at room temperature.

(c) Liquid dextrose

Dextrose hydrate is dissolved in water to yield an aqueous solution, which must be maintained at elevated temperatures (120° to 140° F.) to prevent crystallization.

G. Analytical

1. Methods

(a) Methods of Analysis A.O.A.C., 11th Edition, 1970

(b) Standard Analytical Methods of Member Companies of Corn Industries Research Foundation, a Division of Corn Refiners Association, Inc., 4th Edition

2. Typical analysis - Dextrose monohydrate

Color	White
Form	Dry, crystalline
Taste	Bland, sweet
Odor	None
Moisture	8.5%
Dry Substance	91.5%

3. Chemical Analysis (dry basis) - Dextrose monohydrate

Dextrose	99.2%
Other Sugars*	0.8%
Ash	300 ppm
pH (10% solution)	5.5 - 6.5
Protein (N x 6.25)	None

* Maltose, isomaltose & higher polysaccharides

H. Occurrence

1. Plants

Glucose occurs naturally and in the free state in fruits and other parts of plants. It is also found combined in glucosides, in di- and oligosaccharides, in the polysaccharides cellulose and starch and in glycogen.

2. Animals

Glucose is distributed throughout the animal body in both free and combined forms. Normal human blood contains 0.08 to 0.1% glucose. It is found combined in glucosides, di- and oligosaccharides and glycogen.

3. Synthetics

None

4. Natural Inorganic Sources

None.

V. COMMENTS ON ALL OTHER PHASES OF THE REPORT

The members of the CRA Committee reviewed the material presented in the Scientific Literature Review - Corn Sugar, and evaluated each reference cited in the reviewer's comments. The individual comments of the CRA Committee are summarized in the following compilation. All comments will be made by specific reference to the page and paragraph in Scientific Literature Review - Corn Sugar (PB-223 853).

Page 1, Paragraph 4

Glucose, per se, does not inhibit biliary secretions; the lack of fat in the diet inhibits bile stimulation.

Page 1, Paragraph 4

Wilkins & Kruit (4735) state that crystallization of cholesterol was proportional to the glucose level of human serum. But they also state that cholesterol crystallization was also proportional to the fructose, lactose, galactose and sucrose level. The finding that the rate of crystallization of cholesterol runs parallel to the blood sugar level may be regarded as correct, but because the blood sugar level does not react to glucose alone (but also to fructose, maltose

& sucrose), we cannot accept the inference that cholesterol crystallization rate is caused solely by glucose.

Page 1, Paragraph 5

The Pawan & Tygstrup reference (3329) is irrelevant and should be deleted.

Page 1, Paragraph 6

The Informatics' reviewer concluded that all references to the use of glucose as the standard or control nutrient in testing procedures were not relevant, and therefore not included. The fact that dextrose is often the carbohydrate of choice in control and standard diets by nutritionists and other experimentalists strongly indicates that these scientific investigators have concluded that dextrose has minimum deleterious reactions. Further, the use of dextrose for intravenous injection in hundreds of millions of critically ill patients demonstrates that dextrose is basically free of deleterious reactions when injected into the bloodstream. This evidence supplies strong support to the generally accepted conclusion that dextrose is a completely safe carbohydrate for oral or intravenous ingestion.

Page 2, Paragraph 2

Capellato (688) reports that after many (about 11,000) injections of 25% glucose solutions, two rats showed subcutaneous fibrosarcoma and polymorphocellular sarcoma and one rat a sarcomata in the abdominal cavity. Heupner (1997) found no tumors or other adverse effects after making approximately 22,860 subcutaneous injections. Garsco, et al (1640, 1641), conclude that repeated subcutaneous injections of saline solution, and of water, produces significant tumors, sarcomas, and/or sarcomata at the point of injection. In The Testing of Chemicals for Carcinogenicity, Mutagenicity and Teratogenicity (Health & Welfare Board of Canada, September 1973, p. 9), they state that interperitoneal and intravenous ingestion, "...are not well suited to repeated administration of the compound under test and do not resemble likely conditions of exposure". Further, they also state that, "...regular injection is an arduous procedure and the pathological interpretation may be complicated by local reactions and infections following repeated injections, and perhaps eventually the appearance of subcutaneous sarcoma". In our opinion, the sarcoma observed by Capellato (688) are of very doubtful significance in the evaluation of glucose for use in foods.

Page 2, Paragraph 3

There are too many factors to control in food allergy problems to justify conclusions based on individual clinical histories. Yet the reviewer selects Randolph's investigation (3530, 3531) as the correct reference to state the allergenic status of dextrose. He has chosen to overlook the extensive investigations of Loveless (2630) and does not even cite a reference to the extensive works reported by Bernton (Annals of Internal Medicine, Vol. 36, 1, p. 177-185, 1952). [See Attachments 2 (Loveless) & 3 (Bernton).] Numerous other references are cited by Bernton.

Both Loveless and Bernton conclude that:

1. Sensitivity to whole corn is very low in incidence.

2. Sensitivity to corn starch is rare, even in patients sensitive to whole corn.

3. Sensitivity to refined products made from corn (dextrose, corn syrup, corn oil) cannot be demonstrated by ingestion.

In a more recent reference, (Food Allergy, A. H. Rose, published by Charles T. Thomas, 1972), there is no mention of allergenic reactions after consumption of dextrose.

Page 2, Paragraph 4

The work of Kopfler and Wilkinson (2352) is correctly cited but their observations on day-old chicks has no relevance to the human diet. Selection and quotation of this reference as pertinent is incomprehensible. Further, giving a 40% glucose solution to day-old chickens is disregarding all guidelines for the performance of a scientific test. Chickens react very sensitively to any nutrient substance with a high osmotic pressure and the dose is physiologically high. In addition, data from chicks which have a high metabolic rate and a high ambient body temperature (106° to 107° F.) cannot be extrapolated to the human with any acceptable probability.

Page 2, Paragraph 5

Orcel, et al (3232), examined dextrose as the pharmacon in the L. D. test (lethality tests) and observed liver abnormalities.

Bachman, et al (202), fed dextrose as 68% of the total diet for 10 weeks and compared results to an identical diet containing fructose. Leahy and Allen (78), fed dextrose, corn syrup and sucrose as 80% of the total diet, using a commercial ration as the control. These are abnormally high levels for

feeding refined carbohydrates. Variations were noted between the carbohydrates, but the remarkable aspects of these experiments are that all animals survived, were healthy, grew normally, and showed absolutely no illnesses or clinically significant abnormalities.

The Bachman, et al (202) experiment is not really concerned with correlation of glucose and ulcera, but with the question of whether an emptying stomach may lead to ulceration. Dextrose, a bulk-free agent that is discharged fast, is ideal for this test. Although ulcers were developed in the all-dextrose diet, this does not support the conclusion that dextrose was responsible for the ulceration. Rather, the experiment proves that emptying the stomach may cause ulceration. Further, glucose is never used as the sole nutritive ingredient over a long period of time.

One finding stated in the GRAS monograph on Reference 202 is cited incorrectly. The alleged higher fat content of the liver after intake of glucose is higher in <u>proportion to the liver</u> weight compared with the fat levels of the livers of the controls and of the animals fed fructose. The <u>absolute fat content</u> of the livers of the rats fed glucose is in line

with that of the controls and slightly lower than that of the animals fed fructose. This is due to a higher tissue fluid in the glucose-fed animals.

Page 3

All of the material on this page is concerned with sucrose and has no relevance to a review of dextrose. Further, the reviewer introduces some of his own opinions that are erroneous and irrelevant. All material on page 3 should be deleted.

Page 9, Paragraph 2

The Orcel, et al (3232) reference has little relevance to human nutrition. They administered massive doses far beyond those possible to administer to man. If the g/kg were maintained, 600 gram doses of dextrose would have to be administered intravenously to a 150 pound man. It is remarkable that the rats survived.

Page 9, Paragraph 4

It is remarkable that nine men could be found who could orally ingest 1,000 grams of dextrose in a short time.

Page 10, Paragraph 2

The "liquid glucose" used by Allen and Leahy (78) is really spray-dried corn syrup. The terms "glucose syrup" and

"liquid glucose" usually mean corn syrup, especially by investigators outside Canada and the United States.

Page 11, Paragraph 2

The pig's metabolism of carbohydrates is very comparable to that of man. This work by Becker and Terrill (311) showed complete tolerance and normal growth on a diet containing 50% dextrose.

Page 11, Paragraph 3

Allen, et al (79), present an extremely unrealistic dietary situation in this investigation. The imbalanced diet fed the baboons does not meet recommended NRC-NAS standards for laboratory primates. Furthermore, dextrose was not used in any of the rations and, therefore, the data is not pertinent to the status of dextrose.

Page 12, Paragraph 4

See previous comments on allergy (page 14).

Page 15, Paragraph 2

After review of the relevant literature cited by Portman, et al (3451), it is necessary to conclude that the conclusion that, "...the excretion of bile acids is restrained after intake of glucose..." is not correct.

The suspicion that re-absorption of the bile acids from the small intestine depends on the carbohydrates taken in with the food is qualified by the authors in a later study (O. W. Portmann, Amer.J.Clin.Nutr. 8, 462, 1960). In this second study they find that substances which are hard to digest, such as cellulose and starch, when added to the diet will increase intestinal motility, thus accelerating passage of the faecal matter and excluding a prolonged presence of the bile acids in the lower part of the small intestine. The slower the motility, the longer will the bile acids stay in the small intestine, the more effective will be the re-absorption. As not only glucose but also fructose and sucrose are absorbed quickly, in other words, as they are easy to digest and exert no celluloselike influence on the intestinal motility, the excretion of bile acids after intake of these shortchain carbohydrates is reduced, not restrained.

An increased excretion of bile acids may have a lowering effect on the serum cholesterol level.

On the other hand, the reduced excretion or higher re-absorption of bile acids does not lead to a rise of the serum cholesterol level under normal nutriophysiological conditions.

The absorbed bile acids at a certain bile acid concentration of the portal blood inhibit the bile acid synthesis from cholesterol, the cholesterol store remains "filled" and the cholesterol synthesis is inhibited.

Page 15, Paragraph 4

Sanders (3814) data indicating that fructose inhibits amino acid uptake while dextrose does not is not very convincing.

Page 15, Paragraph 5

Ingestion of glucose is normally expected to effect adrenaline output as reported by Weil-Malherde & Bone (4652). Low blood glucose usually increases output of epenephrine, which then increases other metabolic activities, such as glycogenolysis in the liver and release of glucose into the blood. This is the mechanism that maintains blood sugar levels during fasting. Because all people participating in this experiment had empty stomachs, the adrenaline level had adjusted to maintain a normal blood sugar level. The absorption of glucose and its appearance in portal blood triggers the secretion of adrenaline which metabolizes glucose to glycogen. At the same time, glycogen metabolism is inhibited and the adrenaline is no long used. The rise of the serum adrenaline

level in the venous blood may therefore be regarded as "excess". The fact that adrenaline level of the venous blood does not rise after intake of fructose is attributable to the following:

> In the intestinal mucosa of man, fructose is metabolized to glucose and lactate at a slow rate; the increase in the blood glucose level after intake of fructose is negligible and the secretion of adrenaline must be maintained in order to keep the blood sugar at a normal level. There is therefore no change in the serum adrenaline during the 60 minutes of the test.

Page 16, Paragraphs 3 & 4

Dextrose does not inhibit the crystallization of sucrose, therefore, this property is not "capitalized upon in the manufacture of syrups, confections such as hard candies, jams, jellies, preserves and ice cream". Dextrose is not a foam stabilizer. Because dextrose does lower the freezing point of solutions does not necessarily improve the texture and quality of ice cream.

There appears to be some misinformation or misinterpretation on the part of the reviewer in this regard.

If the F.A.S.E.B. Committee and FDA require information on detailed uses of dextrose as a food ingredient, extensive

lists of recipes, formulas and preparative instructions can be provided by the technical service and sales departments of the CRA member companies.

VI. CONCLUSIONS

The major purpose of the CRA Committee has been to submit to the F.A.S.E.B. Committee and the FDA the most reliable data available. In doing this it has been necessary to refute some of the erroneous conclusions presented by the Informatics, Inc. review.

It is quite evident, based upon the wide use of dextrose as a food, its use in intravenous feeding, its use as an unquestioned standard or reference ingredient in feeding studies, etc., that the scientific community has long regarded it as completely safe as a food for human consumption. As a result of this confidence and lack of any substantive indications to the contrary, there has not been, nor does there seem need for, exhaustive testing of its fitness as a food. It is, after all, the "staff of life", for without it plant and animal life would perish.

Chapter I—Food and Drug Administration

PART 26—NUTRITIVE SWEETENERS

Sec.

26.1 Dextrose monohydrate; identity.
26.2 Dextrose anhydrous; identity.
26.3 Glucose sirup; identity.
26.4 Dried glucose sirup; identity.

AUTHORITY: Secs. 401, 701, 52 Stat. 1046, 1055–1056, as amended by 70 Stat. 919 and 72 Stat. 948; 21 U.S.C. 341, 371.

SOURCE: 38 FR 25986, Sept. 17, 1973, unless otherwise noted.

§ 26.1 Dextrose monohydrate; identity.

(a) Dextrose monohydrate is purified and crystallized D-glucose containing one molecule of water of crystallization with each molecule of D-glucose.

(b) The food shall meet the following specifications:

(1) The total solids content is not less than 90.0 percent mass/mass (m/m), and the reducing sugar content (dextrose equivalent), expressed as D-glucose, is not less than 99.5 percent m/m calculated on a dry basis.

(2) The sulfated ash content is not more than 0.25 percent m/m (calculated on a dry basis), and the sulfur dioxide content is not more than 20 mg/kg.

(c) The name of the food is "dextrose monohydrate" or "dextrose."

(d) For purposes of this section, the methods of analysis to be used to determine if the food meets the specifications of paragraph (b) (1) and (2) of this section are the following sections in "Official Methods of Analysis of the Association of Official Analytical Chemists," 11th Ed., 1970:[1]

(1) Total solids content, 31.005.

(2) Reducing sugar content, 31.212(a).

(3) Sulfated ash content, 31.208.

(4) Sulfur dioxide content, 20.090–20.095.

[38 FR 25986, Sept. 17, 1973, as amended at 39 FR 8158, Mar. 4, 1974]

§ 26.2 Dextrose anhydrous; identity.

(a) Dextrose anhydrous is purified and crystallized D-glucose without water of crystallization and conforms to the specifications of 21 CFR 26.1, except that the total solids content is not less than 98.0 percent m/m.

(b) The name of the food is "dextrose anhydrous" or "anhydrous dextrose".

Attachment 2

ALLERGY FOR CORN AND ITS DERIVATIVES: EXPERIMENTS WITH A MASKED INGESTION TEST FOR ITS DIAGNOSIS

MARY HEWITT LOVELESS
New York, N. Y.

From The New York Hospital and Department of Medicine, Cornell University Medical College

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St. Louis

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(Printed in the U. S. A.)

ALLERGY FOR CORN AND ITS DERIVATIVES: EXPERIMENTS WITH A MASKED INGESTION TEST FOR ITS DIAGNOSIS*†

MARY HEWITT LOVELESS, NEW YORK, N. Y.

THIS symposium on food allergy is the outgrowth of recent widespread medical and lay interest aroused by claims[1,2] that cereals and also their derivative starches, syrups, sugars,[3] oils, and even their grain alcohols,[4] are important excitants of allergy. The subject entered prominently into hearings before the Federal Food and Drug Administration in 1949, when the advisability of labeling salad dressings, breads, and other edible preparations was discussed from the allergenic angle. At this time, Randolph testified that such manifestations as unexplained headache, fatigue, drowsiness, chilliness, and pulling or aching of the muscles might originate from chronic or masked allergy for such regularly ingested foods as corn, wheat, milk, and eggs.

In anticipation of these Washington hearings, the writer interviewed 19 members of the American Academy of Allergy, from various sections of the country, to learn that only 0.12 per cent of their patients were considered susceptible by clinical standards to kernel or ground corn. No convincing instance of hypersensitivity to ingested oil or sugar could be found, and only a rare case of allergy for starch—one being recalled by Spain and another by Walzer. So great was the disparity between these opinions and those of Rinkel, Randolph, and Rowe, that a search for the underlying reason was instituted. Two steps were taken. First, a canvass was made by questionnaire of specialists in allergy and pediatric allergy to gain a more considered and extensive impression of the frequency of corn allergy. Second, an objective diagnostic procedure was devised whereby individuals suspected of hypersensitivity could be subjected to standard feeding tests with whole corn and subsequently with its derivative starch and syrup. The cornstarch pudding employed for the latter could not be distinguished in appearance, taste, or texture from 2 control puddings made of cane-sweetened starch obtained from tapioca or from arrowroot. The aim was to exclude psychogenic and other extraneous factors. These "blindfold" tests were used by 11 allergists on 25 individuals who gave suggestive histories for susceptibility to corn.

MATERIAL AND METHODS

Ingestion Materials: Mush.—As a check on the validity of the history, a feeding of precooked corn-meal mush (degerminated Quaker corn meal), sweetened with "Frodex," a dried corn syrup, was advocated as a preliminary or a final step in the ingestion studies. This ready-to-serve meal was prepared, as were the puddings, by an independent manufacturer in New York City (National Starch Products Inc., to whose Mr. Vincent Marsilia and Miss Mary Bak-

*From The New York Hospital and Department of Medicine, Cornell University Medical College, New York, N. Y.

†Presented before the Sixth Annual Meeting of the Academy of Allergy, Los Angeles, Calif., on March 6-8, 1950.

kovitch the writer is very grateful for their preparation of 67 packages). The mush consisted of 13.6 Gm. of dry meal to which were added 32.1 Gm. of dried syrup containing dextrose, maltose, and such higher sugars as triose and biose. The corn meal in each feeding carried 180 mg. of protein nitrogen and the syrup added another 2.2 mg. As is the case of the puddings, this test meal was posted in a refrigerated carton to the physician just prior to the arrival of the patient, the request being made through the writer's office. Before the next feeding in the series was prepared, all details of the earlier test were in the writer's hands. Each carton was labeled with an individualized code number, so that the patient, his physician, and the author remained in ignorance as to its contents until the entire series had been completed.

The puddings each contained 10 Gm. of starch. In the case of the tapioca and the arrowroot samples, the sweetener was 20 Gm. of cane sugar, whereas 66.6 Gm. of Frodex could be incorporated into the cornstarch pudding with an equal sweetening effect. As flavoring agents, 0.3 Gm. of salt and 0.3 Gm. of citric acid were included in each pudding, 0.03 Gm. of benzoate of soda being added as preservative. When requested, synthetic wild cherry flavoring was also employed in a volume of 6 drops.

The nitrogen content of the cornstarch pudding was estimated at 4.8 mg. protein nitrogen for the starch and 4.2 mg. for the Frodex, giving a total of 9 mg. In the case of the control puddings, the content of protein in their starches being ⅓ to ⅔ that of cornstarch and the sweetener being used in smaller proportion, the total amount of protein nitrogen in the feeding was about 4.2 mg. Hence, the cornstarch meal possessed over twice the protein of the placebo meals and might have been expected, therefore, to be more allergenic if its activity were dependent on contaminating nitrogen.

Ingestion Procedure.—The routine of Rinkel and Randolph was followed as accurately as possible in its several details, corn and its derivatives being carefully excluded from the diet for at least 4 days preceding any feeding. Tapioca and arrowroot, though more rarely ingested, were also prohibited. Wherever it could be safely recommended, the patient took the suspected allergen for 4 days prior to the period of elimination. He came in fasting, was allowed to rest seated for one-half hour before the start of the experiment. All suggestive signs and symptoms were sought and recorded for the 2-hour test period, as well as for the 2-day period before and after the ingestion. The subjects were also advised to avoid, or at any rate to record, any exposure to drugs, allergens, or other factors which might color the outcome of the test.

FINDINGS

Incidence of Allergy for Whole Corn (Kernel or Meal).—Table I is based on the replies received from 56 physicians who answered the questionnaire. The data have been segregated according to the frequency with which allergy for whole corn was encountered. For 45, the incidence amounted to only 0.16 per cent, or 1 case in 600, among a population of 45,500 individuals. Five additional physicians reported 82 cases in a total of 5,200 patients, giving an incidence 10 times higher and doubling the over-all figure. Another 4 found

59 instances in 1,700, bringing the average to 0.39 per cent for a population of 52,500 subjects.

The findings of the last 4 contributors are individually listed since they differ strikingly from the others. Rinkel, for example, has published a study of 200 patients with suspected hypersensitivity for whom he diagnosed corn as the etiologic factor in 16 per cent. We have taken the liberty of multiplying this population by 5 to make it comparable with those covered by the questionnaire. The same step was taken for Randolph who reported an incidence of 20 per cent in a group of his hypersensitive subjects at the 1949 hearing before the Food and Drug Administration. Rowe's response to the questionnaire was that he encountered 25 to 30 per cent of such cases among 1,200 patients. Finally, Crandall recorded 170 instances among 565 subjects, an incidence of 30 per cent.

It will be noted that the last 4 clinicians make the diagnosis of corn allergy about 100 times more frequently than the average allergist represented by the first group. It is hoped that some possible explanations for this disparity will be found in the results of our experiments with controlled feeding, to be presented below.

TABLE I. INCIDENCE OF CLINICAL ALLERGY FOR WHOLE CORN OR CORN MEAL

ALLERGISTS	PATIENTS OBSERVED	NO. CORN-ALLERGIC	INCIDENCE (%)	CUMULATIVE TOTALS		
				PATIENTS OBSERVED	NO. CORN-ALLERGIC	INCIDENCE (%)
45*	45,573	75	0.16	45,573	75	0.16
5*	5,220	82	1.57	50,793	157	0.30
4*	1,700	59	2.88	52,493	216	0.39
Rinkel†	1,000	160	16.0	53,493	376	0.7
Randolph†	1,000	200	20.0	54,493	576	1.0
Rowe	1,200	300	25.0	55,693	876	1.57
Crandall	565	170	30.0	56,258	1,046	1.86

*Members or Fellows of the American Academy of Allergy of whom 15 were certified internists; 3 were certified pediatricians.

†From the August-September, 1949, Hearing before the Federal Food and Drug Administration.

Ingestion Studies.—Table II summarizes the findings of ingestion tests carried out on 25 individuals who gave a history suggestive of allergy for whole corn. The data have been segregated into 3 sections, depending on the clarity of the diagnosis. Group A refers to 13 individuals whose allergy seemed the most certain, confirmation of the history being found by means of ingestion tests with our standard mush meal in 5 instances, with feeding tests devised by other allergists in 5 other cases, and on the basis of convincing histories for the remaining three. Details for the experiments on all but two of the members of this group are to be found in the recorded hearings before the Food and Drug Administration of 1949 as well as in the current issue of this journal under the investigators' names.

The outcome of experiments with these 13 clear-cut instances of corn allergy can be briefly summarized in the following statements. Eleven of the subjects gave entirely negative responses to masked feedings with cornstarch. Of the 2 who reacted to the cornstarch puddings, one (JM) did so on one occasion but failed to do so during an earlier ingestion experiment. The manifestation, consisting of abdominal cramps which occurred 7 hours after the feeding, was of

moderate severity and lasted for 4 hours. The first trial had elicited only a suggestion of "gassy indigestion" after 10 hours. In contrast, the standard mush feeding had provoked marked cramps within one-half hour. Had the pudding test been reproducible, one could have accepted this as an example of cornstarch allergy, attributing the relative delay in symptoms to the lesser amount of protein in the cornstarch as compared with whole corn meal. The lack of reproducibility, however, somewhat weakens one's convictions.

The other instance of cornstarch reaction was much more convincing. Patient MB developed asthma of moderate intensity within 1 hour of receiving a pudding, later identified as containing cornstarch. After 7 days, another such pudding reproduced the manifestation in marked form and a third experiment confirmed the diagnosis of cornstarch allergy. This woman showed unmistakable reactions to whole corn meal, developing prompt contact responses of the mouth and throat as well as immediate severe asthma.

Tapioca sensitivity was noted in one of the 13 patients of Group A, the patient being MB referred to above. She experienced severe asthma within 1 hour after the masked feeding on one occasion and promptly after ingestion on another.

Arrowroot starch caused a moderately severe gastrointestinal disturbance in 1 patient, and mild asthma in another. The first subject was observed by Shulman who reported that diarrhea had occurred in 48 hours and had lasted 2 hours, after she had been given the arrowroot pudding. Rawling's patient felt somewhat nauseated at once and became mildly asthmatic within one-half hour. Both symptoms subsided quickly. The long interval involved in the first instance and the mild, transitory nature of the reaction in the second patient weaken the interpretation of these findings as evidence of allergy to arrowroot.

Of these 5 instances of response to the starch puddings, only 2 are really convincing, those of the patient, MB, who reacted to both corn and tapioca. If so few cases are to be found among a group of patients of such highly selective character, the incidence must indeed be low among the general population. The suitability of the 13 individuals in Group A for the feeding experiments with cornstarch is made evident by their unequivocal clinical sensitivity toward whole corn. Table II reveals that 5 of them developed marked asthma, 7 various degrees of gastrointestinal disturbance, 8 nasal manifestations of allergy, 2 urticaria or atopic eczema, and 1 marked headache. With the possible exception of the latter, all these are classical expressions of allergy. Furthermore, they occurred promptly after the cereal had been eaten, 9 being noted within one-half hour and the rest within 5 hours. Although headache is a borderline manifestation, in the case of Sheldon's patient it was evoked in 30 minutes and was of extreme severity, so that it could be accepted as presumably allergic in origin.

Concerning the other derivatives of corn, none of the 11 individuals tested with syrup, sugar, or oil gave any sign of untoward effect, even on repeated feedings. One patient was also negative to the intravenous administration of dextrose. The involvement of cane sugar can be excluded from consideration since each of the several subjects responding to 1 starch pudding was fully tolerant of the other pudding which contained the same sweetener. This also applies to the flavoring and preservative used in all puddings.

TABLE II. INGESTION RESPONSES TO WHOLE CORN, CORNSTARCH, SUGAR, SYRUP, AND OIL IN PATIENTS SUSPECTED OF HAVING CORN ALLERGY

PHYSICIAN	PATIENT	RESPONSE TO INGESTION OF WHOLE CORN: BASIS OF DIAGNOSIS	SYMPTOMS: ASTHMA	G.I.	NASAL	SKIN	HEADACHE	ONSET IN HRS. P.C.	RESPONSE TO STARCHES & CORN PRODUCTS: CORN-STARCH	TAPIOCA	ARROW-ROOT	CORN SYRUP	CORN SUGAR	CORN OIL
Group A: 13 Patients With Excellent Ingestion Result and/or History for Corn Allergy														
Sheldon	1*	Trial		++	++			½	0			0	0	0
Sheldon	2*	Trial			++		+++	½	0			0		0
Sheldon	3*	History	+++					½	0			0		
Sheldon	4*	Trial		+	+			¼	0,0			0		
Sheldon	5*	History		+++	++			¾	0			0	0	
Sheldon	6*	History			+++			1	0			0	0	0
Rawling	1*	Trial	+++		+ eye			3	0†		0†		0	0
Cazort	KEP†	Mush†		+++		+		¼	0†	0†	0†	0	0	0
Halpin	CH*	Trial	+++	+++		+++		¼	0† 0†		0†	0	0 i.v. 0	0
Bernton	2*MB	Mush†	+++					¼	+++† +++† +++†	+++† +++†	0†	0	0 0 0	0 0
Conn	JK	Mush†			+++			5	0†	0†	±†			
Shulman	JM	Mush†		+++				½	±† ++†	0†	++†			
Rawling	2	Mush†	+++	+	+			½	0†		+†		0	0
Total	13	5 Trial 5 Mush†	5	7	8	2	1	¼-5	2 pos.	1	2	9 neg.	8 neg.	8 neg.
Group B: 10 Patients With Fair Ingestion Result and/or History for Corn Allergy														
Bernton	1*	Mush†			+				0†					
Lazar	PB	Mush†	+++					6	0†	0†	0†			
Black	CB	Mush†	++					12	0†	0†	+†			
Altose	BC	Mush†	+		+			3½	++†	±†	±†			
Altose	JS	Mush†			++	++		24	+++† +++†	+†	0†			
Cazort	LO	History	+++	++				chronic	0†	0†	0†			
Cazort	MCK	History	+++			++			0†	0†	0†			
Cazort	RU*	History	+++	+++				2-3	0	0	0	0		0
Cazort	AR	Starch History?	+++			+++		12	+++†					
Black	WBC	History				++		12	0†	±†	±†			
Total	10	5 Mush†	7	2	3	4		2-24	3	1	1			
Group C: 2 Patients With Possible History but Negative Ingestion Test														
Loveless	AN	Mush†	0				0		+†	++† 0	++† 0			
Loveless	AHR	Mush†					±		++† 0† 0†	±†	±†			
Grand Total	25	12 Mush† 5 Trial	12	9	11	6	1	¼-24	7	3	4	10 neg.	8 neg.	9 neg.

*Details presented before Federal Food and Drug Administration in August and September, 1949.
†Loveless standard meal (mush or pudding).

These findings confirmed the claims of Rinkel and Randolph and the observations of Walzer and Spain that cornstarch can act as an ingestant allergen, rather to the surprise of the investigating physicians. The starches of tapioca and probably also of arrowroot can play a similar role. The convincing example found in Bernton's patient can be examined in detail in the August-September hearings of the Food and Drug Administration for 1949 and seen in synoptic form in Table III.

TABLE III. INGESTION STUDIES ON ASTHMATIC PATIENT, MB (BERNTON)

MATERIAL INGESTED	AMOUNT FED (GM.)	NO. OF TRIALS	ASTHMA INDUCED	INTERVAL IN MIN.
Corn meal*	13.6	1	+++	several
Dextrose	12.0	3	0	
Cornstarch*	10.0	3	++,+++	3 - 55
Corn oil	30.0	2	0	
Corn syrup	30.0	2	0	
Arrowroot starch*	10.0	3	0	
Potato starch*	10.0	1	0	
Tapioca starch*	10.0	2	+++	15 - 55

*Loveless standard pudding or mush.

The failure of most patients in this group of definite whole corn sensitivity to react to cornstarch can be demonstrated by the case of Halpin. This 27-year-old woman gave a history of immediate edema of lips and tongue as the result of ingesting kernel and ground corn on 2 occasions. Severe urticaria, dyspnea, cough, and wheeze shortly developed and were followed by diarrhea and collapse which required 3 administrations of epinephrine for their control. The standard mush feeding was contraindicated in this severe case. The subject submitted to pudding tests with cornstarch on 2 occasions and with arrowroot on 1, and remained symptom-free. She not only tolerated ingestions of corn syrup, corn oil, and corn sugar but also took the latter by vein equally well. These findings are summarized in Table IV.

The young college student, KE, of Cazort is another example of extreme hypersensitivity toward kernel corn in combination with complete tolerance for large doses of each derivative by mouth. In keeping with his history, mush provoked immediate "tingling, burning, and a thick feeling in the mouth and throat." Severe abdominal cramps and urticaria were present some hours later. On the contrary, no untoward effects followed the taking of masked puddings in which the starches of corn, tapioca, or arrowroot were present. Similarly, corn oil, syrup, and sugar were taken in masked form without incident.

Six other individuals gave equally convincing results when tested by Sheldon with his own types of masked feeding. All these clearly corn-reactive patients proved to be fully tolerant of the starch and syrup of corn, and those given corn sugar and oil were similarly negative. Patient 1, investigated by Rawling with his own method of trial feeding with whole corn, like that of Conn who employed our standard mush, is an acceptable member for Group A in spite of the somewhat delayed appearance of manifestations. Both individuals were given cornstarch pudding, as well as 1 or more control puddings, without significant effect.

Table IV. Ingestion Studies on Patient C. by Dr. Halpin

Date	Preceding Symptoms	Material Ingested	Symptoms: Asthma	Nausea	Diarrhea	Urticaria	Edema
1946	0	Corn bread†	+++ onset ¼ hr.	+++	+++	+++ ¼ hr.	+++*
		Corn on cob†	+++ ¼ hr.	+++	+++	+++ ¼ hr.	
1948	0	Glucose 10 % intravenously	0	0	0	0	0
		Corn oil	0	0	0	0	0
		Corn sugar	0	0	0	0	0
		Corn syrup	0	0	0	0	0
7/27/49	0	Cornstarch	0	0	0	0	0
1/10/50	0	Cornstarch	0	0	0	0	0
6/29/49	0	Arrowroot	0	0	0	0	0

*Lips and tongue.
†Small portion of a serving.

Table V. Ingestion Studies on Patient AN

Date	Preceding Symptoms	Material Ingested	Symptoms: Asthma	Asthma Hrs. P.C.	Headache	Headache Hrs. P.C.	Fatigue	Fatigue Hrs. P.C.	Vertigo	Vertigo Hrs. P.C.
11/23/49 10:30	0	Mush*	±	¾ - 1¼	0		0		0	
12:40	0 for 1 hr.	Corn on cob	±	¼ - 2¼	0		0		0	
11/18/49	0	Corn starch*	+	1 - 5	0		+++	½ - 4½	++	5⅓ - 6
11/9/49	Fatigue ++	Arrowroot*	++	3 -	0		0		0	
12/2/49	0	Tapioca*	++	1 - 2½	0		0		0	
1/31 /50	0	Tapioca	0		0		0		0	
2/3/50	0	Arrowroot crackers	0		+++	¼ - ½	0		0	
2/8/50 10:00	Asthma ±	Saline 1 c.c.	+	½ - 1¾	+	¼ - 1¾	0		0	
11:45	Asthma ±	Saline 1 c.c.	+	½ -	+++	5 min. - 1	+	1 -	0	

*Loveless standard test meal.

When these 2 experiments are included with those described above for Group A, it is apparent that the large proportion of patients clearly susceptible to whole corn is unquestionably tolerant of its derivative starches and sugars, this being the observation for 11, and possibly 12, of the 13 test subjects.

Group B furnishes less valuable evidence because in general its responses to ingested corn were either mild in degree or delayed in development. Five of its members were diagnosed by ingestion test with our standard mush, whereas the history alone was used as the basis for diagnosis for the other 5. In spite of these shortcomings, some weight may be placed on the negative responses of 7 of the subjects to cornstarch and to such other corn derivatives as were employed. The anomalous situation encountered in the experiments with 2 of the patients, who appeared more reactive to starch than to meal, is worthy of further investigation. The third case listed as positive for cornstarch by the pudding test is difficult to interpret both from the viewpoint of the feeding result and the history. This 30-month-old baby (AR) was suspected of being cornstarch-allergic by its mother and was known to be reactive to both corn and cottonseed flours by inhalation. The only ingestion experiment done was one with cornstarch pudding. Three hours later a few hives had developed on the knee, and by 12 hours the eruption was generalized and mild asthma was present. The latter became so severe by the next morning that the child was hospitalized. It was unfortunate that control and whole corn ingestion studies were refused after this development.

Group C was composed of 2 of the author's patients who deserve brief mention because their symptoms resembled those classed as allergic by Randolph but not generally accepted as such by the profession. These responses were elicited by the derivatives but not by whole corn.

Table V summarizes the findings with An, a woman who was having asthma almost daily which was considered to be caused by several danders, house dust, and foods. After her first ingestion test with arrowroot pudding, she suffered an attack of moderately severe asthma. Nine days later the ingestion of cornstarch pudding was shortly followed by marked fatigue and mild asthma. After their disappearance some 4 hours later, a short spell of vertigo was noted. Her subsequent examination with standard mush and fresh kernel corn failed to duplicate these manifestations aside from a suggestion of mild asthma, which was surprising in view of the fact that larger doses of the hypothetical allergens in corn must have been involved. Interpretation of this woman's reactions was again made difficult by her failure to develop, at home, symptoms of asthma which followed the taking of tapioca in the office. Furthermore, arrowroot appeared to elicit asthma of moderate severity 5 hours after she ate a masked pudding under our observation but when she tried arrowroot crackers at home a severe, brief headache was the result. Suspecting by now that factors other than our test meal allergens were operative, we subjected her to a feeding experiment with saline solution which she believed to be an allergenic extract. This gave rise to mild asthma by 30 minutes and to headache almost immediately. Fatigue of slight degree was also reported. Without the repeated tests and the saline control, this woman would have been considered allergic to all 3 of the starch puddings, especially if the diagnosis had been guided by the criteria of Rinkel and Randolph.

For comparable reasons, one might have been misled by the initial cornstarch reaction of AII. His persistent fatigue was increased as also was his headache by this masked pudding test. Repetition of the ingestion in 2 weeks yielded a negative result except for a suspicion of fatigue. Still a third experiment provoked no complaints whatsoever. These 2 essentially negative responses to cornstarch are consistent with his tolerance of both mush and kernel corn. It was important to the understanding of this case that repeat tests be carried out.

DISCUSSION

A survey of 56 allergists and pediatric allergists throughout the country revealed that for all but a few physicians clinical allergy for whole corn is a rarity which is encountered 100 times less frequently than Rinkel, Randolph, Rowe, and Crandall have reported. Some explanations for this disparity have been uncovered by our experiments with objective feeding tests. It was found that extraneous factors, especially of psychologic origin, can complicate the diagnosis unless the patient is subjected to repeated studies, to masked ingestions, and to placebo meals.

Whereas no evidence was found for the allergenicity of corn oil, syrup, or sugar, clinical reactions were, to our surprise, encountered following the controlled ingestion of the several starches employed for these studies. The clinical significance of this type of hypersensitivity would not appear, however, to have the practical importance assigned to it by Randolph and his school. For one thing, its occurrence was rare even among our group of patients who were selected on the basis of their marked allergy for whole corn and who were tested with relatively huge ingestant doses of starch. Randolph has claimed that provocative amounts of starch allergen escape from paper cartons into milk, sauerkraut, and frozen foods. It seems unlikely that our cornstarch-reactive cases would have been affected by such traces. At any rate, the incidence of clinical susceptibility ought to be far lower with such small amounts of this substance than with the 10 Gm. of cornstarch involved in our puddings.

Presumably any allergenicity of starch, syrups, and sugars would be referable to contaminating proteins carried along from the whole cereal into the derivatives. Starch itself would probably not be antigenic in view of its prompt breakdown into smaller molecular substances by enzymes present in all biologic fluids. Furthermore, the proteins of whole corn would also be reduced considerably in activity because of the drastic treatment involved in the preparation of the derivatives, including heating and strong acidification.

Theoretically, bacteria might play a role in contributing antigens to corn derivatives. It is known, for example, that *B. macerans* is introduced during the preparatory process. In addition, it might be found that this organism, like the streptococcus, can synthesize dextrans, which have been shown to possess immunological activity.[5] Before any of these thories can be accepted, it will be necessary to support them by controlled experimental evidence.

It would seem that the chief cause of the disagreement among allergists concerning the frequency of food allergy must relate to the diagnostic criteria employed. The individual feeding procedures of Rinkel and Randolph, as well as

the elimination diets of Rowe, were introduced because the cutaneous test was found to be unreliable in this type of hypersensitivity. Although they constitute a step in the right direction, these methods fail to take into account the influence of extraneous factors, particularly those of psychologic origin. Consequently, an abnormally high incidence of positive results would be expected. Furthermore, there has recently been added to the diagnostic list a considerable variety of new symptoms. Although such an increase in the scope of allergy may eventually be found justifiable, this can only be decided after a scientific diagnostic procedure has been devised. To attempt to set up a new method simultaneously with the introduction of new symptomatology is tantamount to testing the validity of one unknown by the use of another. There is, then, an urgent need at the moment for the creation of an adequate diagnostic technique. The adequacy should be firmly established by its application to only those patients whose diagnosis is unequivocal. The members of Group A fulfilled this requirement in the "blindfold" ingestion procedure described in this article, their diagnoses resting on the speed and classical form of their reactions to whole corn. It is true that the psychologic factor was not excluded due to the impossibility of masking the characteristic taste and appearance of the unrefined cereal. However, the mush feeding was only a screening technique to confirm a straightforward history, and the psychologic factor was effectively controlled in the masked ingestion procedure associated with the pudding tests for starch and sugar allergy.

SUMMARY

1. A poll of allergists revealed that clinical symptoms from ingested corn were encountered in only 0.16 per cent of their 45,000 patients. This stands in marked contrast to an incidence of 16 to 30 per cent reported by Rinkel, Randolph, Rowe, and Crandall.

2. "Blindfold" ingestion studies associated with placebo meals were done in 25 patients with histories suggestive of corn allergy. A few instances of reaction to large feedings of the starches of corn, tapioca, and arrowroot were encountered, but no case of susceptibility for corn syrup, sugar, or oil. The symptoms of several patients were found to be psychogenic rather than due to the suspected food.

3. An appeal is made for the introduction of controlled, objective methods to the study of food allergy.

The writer wishes to thank the physicians who cooperated to make this study possible, and to acknowledge aid of Misses C. Spearing and A. Ryan as well as Mrs. H. Rice.

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Attachment 3

FOOD ALLERGY WITH SPECIAL REFERENCE TO CORN AND REFINED CORN DERIVATIVES

By HARRY S. BERNTON, M.D., F.A.C.P.

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FOOD ALLERGY WITH SPECIAL REFERENCE TO CORN AND REFINED CORN DERIVATIVES *

By HARRY S. BERNTON, M.D., F.A.C.P., *Washington, D. C.*

AT a hearing on "Bread Standards," held during the summer of 1949 before the Federal Security Administrator, consideration was given to the possible allergenic ingredients of bread, including corn and the refined corn derivatives. The testimony revealed a sharp difference of opinion regarding the incidence of sensitiveness to corn among the allergic population. The divergence was so marked as to justify an inquiry into the present status of allergy to corn and to present additional and pertinent experimental evidence.

Dr. Theron G. Randolph testified that corn was second only to wheat as a specific cause of chronic food allergy. He stated, moreover, that one out of every five of his new patients (or 20 per cent) was found to be corn-sensitive. Confirmation of this high incidence came from the reports of Zeller and Rowe. Zeller had encountered 30 to 40 corn-sensitive patients during the past year, whereas Rowe had found 20 to 35 per cent of 1,200 patients allergic to corn.

Randolph and Yeager,[1] in a later publication, not only reëmphasize the high incidence of corn sensitivity but also include some of the refined corn derivatives as causes of corn allergy. In treatment, they recommend the avoidance of corn starch, corn sugar and corn syrup. They even urge a careful investigation of the current widespread use of corn syrup in infant feeding, implying thereby that corn syrup may become a sensitizing factor in infancy. "Corn is, by all means, the most difficult food in the American diet to avoid," these authors assert. If, therefore, 20 per cent of our allergic population are to be adequately protected, they must be denied an important food and its derivatives which are omnipresent in the American diet. Moreover, the widespread use of corn starch and corn sugar in such unsuspected articles as milk cartons, frozen food containers and excipients presumably adds to the menace.

At the hearing, dissenting opinions regarding the alleged high incidence of sensitiveness to corn were voiced by five allergists. Rawling, in a study of 1,250 case records, discovered only 15 patients (or 1.2 per cent) with corn sensitivity, indicated either by skin or by ingestion tests or both. Sheldon testified that he had given corn starch, corn sugar, corn syrup and corn oil to six patients proved

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From the Allergy Clinic, Providence Hospital of Washington, D. C.

clinically sensitive to corn meal by the ingestion test. He was unable to produce allergic symptoms by feeding the corn products. Cazort's findings were identical with those of Sheldon in feeding corn starch, corn oil and corn syrup to two patients very sensitive to corn meal. Halpin had encountered approximately 15 patients clinically sensitive to corn meal from 1946 to 1949. During this period he had seen, on an average, 350 to 400 new patients each year. Feeding tests performed with one corn-sensitive patient by the "blindfold" technic failed to reveal a sensitiveness to corn starch and dextrose. Rawling also reported that the experimental feeding of corn starch, corn syrup and corn oil to a corn-sensitive patient provoked no allergic reaction. In summary, it may be stated that four allergists have been unable to reproduce symptoms by the experimental feeding of corn derivatives to a total of 10 patients sensitive to corn meal.

The findings from a questionnaire which had been submitted by Dr. Mary H. Loveless to experienced allergists of the country also assume significance. Nineteen physicians reported that they had tested within a recent five year period approximately 35,826 patients for sensitiveness to corn meal and that, among this number, 56 cases had been found clinically sensitive to corn, the percentage being 0.12. Furthermore, the experience of Walzer, as indicated in his reply to the questionnaire, is noteworthy. He writes: "Corn meal reactions are frequent, and may be strongly positive. . . . Reactions to corn by passive transfer are as common as by direct testing. . . . Corn starch reactions are extremely uncommon, even when strong corn meal reactions are obtained. We can recall only one corn starch reaction obtained by passive transfer, despite the high number of corn meal reactions obtained with this technic."

Our experience also shows that the incidence of cases with significant symptoms of sensitivity to corn or to corn derivatives has been very much lower than that recorded by Randolph, Zeller and Rowe. In an analysis of 2,431 patients under my observation and tested for corn, 301 (or about 12 per cent) gave positive cutaneous reactions. Of 306 patients who associated some of their symptoms with sensitiveness to foods, nine (or about 3 per cent) attributed their distress to the ingestion of corn.

A recent noteworthy contribution to the study of foods in respiratory allergy has been made by Leibowitz, Chester and Markow.[2] These authors performed 3,920 skin tests by the intracutaneous method with 56 individual food extracts on 70 patients. The skin tests, irrespective of their results, were followed by intentional feeding tests with all the foods employed. Each food was eliminated from the diet of the patient for one week prior to the ingestion test. Thirty-three of the 44 patients who showed a positive skin test with corn were subjected to the feeding test, with two positive reactions. In the case of the 26 patients who reacted negatively to the skin test, 15 feeding tests with corn all proved negative. Thus, two patients in a total of 48 (or 4.1 per cent) gave evidence of clinical sensitiveness to corn by the ingestion test. Only one patient, however, in a total of 54 (or 1.8 per cent) reacted positively to the ingestion test with corn meal. In this latter group, there were 37 positive and 33 negative skin reactors. The authors conclude that food plays a minor rôle in the causation of respiratory allergy. The discrepancy in the incidence of corn allergy as shown by the foregoing reports was, indeed, as distressing as it was challenging.

The purpose of the present study is to supplement the one I have previously

made and to determine the incidence of sensitiveness to corn derivatives among those found to be sensitive to corn meal by the application of the Randolph technic.

The limitations of clinical history and of skin tests for the diagnosis of food sensitiveness have been fully recognized. Agreement is universal that the ingestion test offers more accurate and specific means of diagnosis of food allergy. The test food is ingested on a fasting stomach after a period of four days of abstinence from that food. The symptoms provoked by such ingestion are determined by the affected "shock organs"—the respiratory tract, the gastrointestinal tract or the skin. It follows, therefore, that sensitiveness to corn allergens in the corn derivatives—dextrose, corn starch, corn syrup and corn oil —can only be determined by the ingestion test in an individual who has been proved sensitive to corn meal.

In my preliminary experiment,[3] 50 consecutive cases were subjected to the ingestion test with corn meal following a prescribed preparatory period. Only two of my patients (or 4 per cent) reacted positively. Despite the small series, the findings are significantly low. The supplementary phase of the study, that of sensitiveness to corn derivatives, was made possible by the unusual coöperative effort of one of my patients.

Case History

The subject who coöperated in the present investigation was a 37 year old woman with a history of allergy on the paternal side. Her chief complaint was asthma of 11 years' duration. The symptoms were perennial and were aggravated from July to October. Provocative causes were "taking cold," excitement, emotional stress and fatigue. Exposure to drafts, air-cooled environment, electric fans and dust "choked her up." She was sensitive to aspirin and to the iodides: the former produced "indigestion," the latter pain in the jaws, as if she had mumps. The eating of corn and lima beans was immediately followed by choking sensations. The symptoms were prompt in appearance, and she adds: "The first spoonful of corn will choke me up." In fact, the steam arising from boiling corn would excite an asthmatic paroxysm, whereas steam from other foods had no deleterious reaction. Eating corn starch custards would produce symptoms which were "not real bad." She had not used corn oil or syrup. She was fond of corn and lima beans but had excluded these foods from her diet because of their ill effects.

During the initial visits of our patient to the clinic, cutaneous tests for protein sensitivity were performed as a matter of routine. Of all inhalant allergens, the pollen of the English plantain reacted positively. The food extracts, including corn, gave negative reactions. With the renewal of our interest in her clinical sensitiveness to corn and possibly to derivatives of corn, a revised list of potential allergens was used on August 9, 1949, for the determination of skin sensitiveness. The list was comprised of the following: corn meal (Indian Head), corn meal (Mammy Lou), corn oil, corn starch (Argo), allergen extract of corn meal, cottonseed oil, rye flour and whole wheat. The eight test substances were applied to scratches on the skin of each thigh. The site of the corn starch presented an areola which gave rise to a slight itching sensation. All the other tests were negative. Again on April 28, 1950, two extracts of corn meal and zein, in powdered form, gave negative skin reactions in a duplicate series. On May 12, 1950, zein was reapplied to scratch marks on the skin, with negative result. The patient was kept under observation for an hour after the test. It is significant that no constitutional reaction ensued in a subject as sensitive as she was subsequently determined to be, by the absorption of the chief protein isolated from corn meal.

Feeding Tests. Results

In the series of feeding experiments in which the patient participated, she was never advised of the nature of the food given to her. Herein is an important modification of the Randolph technic. It was deemed essential to minimize all psychic factors.

On July 12, 1949, the first ingestion test was performed. The patient was instructed to abstain from the consumption of corn, corn products and corn derivatives during the four days preceding the test. A list of permissible foods was furnished, as well as a blank sheet for recording the articles of foods ingested during the preparatory period. On the morning of the test the patient, having been previously admonished not to take any food, drink or medicine, was offered four ounces of warm corn meal mush. After swallowing one teaspoonful of the corn meal she experienced an itching of the lips and immediately developed severe asthma. The administration of 0.4 c.c. of adrenalin and of 7.5 gr. of caffeine sodium benzoate brought gradual and complete relief.

Table 1 lists nine experimental feeding tests, performed with corn meal mush, corn starch pudding, corn oil, corn syrup, arrowroot pudding and peanut oil. Each feeding test with a corn derivative was repeated at a subsequent time. The test

Table I

Feeding Tests; Identity of Food Unknown to Patient

Date of Feedings	Ingestant	No. of Feedings	Reaction
1949			
July 12	Corn meal mush	1	Asthmatic attack
July 26	Corn starch pudding	1	Asthmatic attack
July 29	Arrowroot pudding	1	Negative
Aug. 5	Corn starch pudding	1	Asthmatic attack
Aug. 10	Peanut oil	1	Negative
Aug. 12	Corn oil	1	Negative
Aug. 26	Corn oil	1	Negative
Sept. 2	Corn syrup	2	Negative
Nov. 22	Corn syrup	2	Negative

feeding with each article was performed on a fasting stomach after a four-day period of abstinence from the derivatives of corn. The identity of the test food was not disclosed to the patient.

The ingestion of corn starch on July 26 and August 5 was followed by asthmatic attacks in 18 and 15 minutes, respectively. The administration of adrenalin was necessary to bring relief. The ingestion of 20 c.c. of peanut oil, of four ounces of arrowroot pudding, of 30 c.c. of corn oil and of 60 c.c. of corn syrup at two different trials was not followed by allergic disturbances.

Table 2 includes six feeding experiments with puddings, the identity of which remained unknown to me until after the completion of the series. Four ounces of pudding were consumed at each serving. Two feedings of arrowroot pudding and one of potato starch pudding gave rise to no symptoms. Two feedings of tapioca pudding and one of corn starch provoked asthmatic seizures which required the injection of adrenalin for relief. This second series of experiments not only confirmed the patient's sensitiveness to corn starch but also disclosed a sensitiveness to tapioca. Interestingly enough, when advised of this unexpected finding the patient commented that she had not eaten tapioca to her knowledge for at least 20 years.

In the period from July 22, 1949, to February 21, 1950, the following 15 feeding

tests were performed with our patient: one with corn meal mush, three with corn starch pudding, three with arrowroot pudding, two with tapioca, one with peanut oil, one with potato starch, two with corn oil and two with corn syrup. The corn meal mush, the corn starch and the tapioca were regarded as allergenic offenders because, upon ingestion, each gave rise to asthmatic symptoms. Ingestion of corn oil and corn syrup, arrowroot pudding, peanut oil and potato starch did not produce allergic manifestations. The ingestion tests were all performed on a fasting stomach after a preparatory period of abstinence from corn and corn derivatives.

The above tests emphasize the limitations of cutaneous testing for food sensitiveness and indicate that cutaneous sensitiveness and mucosal sensitiveness are distinct entities.[4] This difference was illustrated when some powdered corn starch was applied on the inside of the lower lip of our subject. Within a very few minutes she began to "choke up." Thirteen minutes later, the starch was removed and the mouth rinsed. There was a gradual subsidence of her discomfort. One week later, a large granule of starch was placed on the inside of the right cheek. Slight coughing ensued. Fifteen minutes later, the coughing was accentuated, and breathing became labored. After 65 minutes, the starch was a paste, the mucosa was normal in appearance and the dyspnea had increased, necessitating the use of adrenalin. The

TABLE II

Feeding Tests; Identity of Food Unknown to Dispenser and Patient

Date of Feedings	Symbol	Ingestant	Reaction
1950			
Jan. 25	E 1	Tapioca	Asthmatic attack
Feb. 3	F 1	Arrowroot pudding	Negative
Feb. 7	C 1	Potato starch	Negative
Feb. 10	F 1	Arrowroot pudding	Negative
Feb. 13	A 1	Corn starch	Asthmatic attack
Feb. 21	E 1	Tapioca	Asthmatic attack

patient reported that later on in the afternoon she experienced a feeling of soreness on that portion of tongue and cheek which had been in contact with the starch granule. She also noted in that area four "small blisters" which disappeared by morning.

The determination of a reagin for corn in the blood serum of our subject was next undertaken. Seven individuals were each sensitized with her blood serum and with 0.05 c.c. of serum from a cottonseed-sensitive patient as a control. The sensitized sites of four recipients were each tested by intracutaneous inoculation with a corn extract. The results were negative.

The other three recipients were subjected to a feeding test. Six ounces, eight ounces and 10 ounces of corn meal mush respectively, were consumed by each person on a fasting stomach. The skin sites, sensitized with the serum from our corn-sensitive patient, remained unchanged. Thus, by feeding test and direct testing of sensitized sites, there was disclosed no evidence of a specific reagin for corn meal. The recipients were instructed to abstain from eating corn and corn derivatives for a period of four days prior to sensitization and for three days following inoculation with the test sera.

The allergen in the corn meal, whatever its nature may be, exerted no harmful influence upon the gastric mucosa. It caused no nausea, vomiting or diarrhea. The allergen was readily transported by the blood stream to the reaetive or sensitized cells of the respiratory tract, with resulting upheaval.

Discussion

Consideration must now be given to the alleged potential allergenic properties of corn derivatives—dextrose, corn starch, corn syrup and corn oil. Randolph's views [5] are summarized in his testimony as follows: "The treatment of food allergy consists in the complete avoidance of the specific foods diagnostically incriminated; in the majority of instances when dealing with the high degrees of sensitivity this means the avoidance of the particular food in its native form, as found in the native form cooked and in addition fractions of the food such as the starch and sugar derived from that food. In some instances it is also necessary to avoid the oil of the food in question in order to relieve specific allergic symptoms. . . . In the first 100 cases, corn sensitivity was diagnosed by feeding canned corn or corn meal gruel. In the second group of 100 cases, corn meal gruel plus corn sugar was used as the test food. The results of these two series indicate that the addition of corn sugar increased the incidence and severity of allergic symptoms occurring during the course of experimental food tests for detection of corn sensitivity."

It is evident from current practice that the allergenicity of corn sugar or glucose has been totally disregarded. The intravenous administration of 1 to 3 L. of a 10 per cent solution of glucose to dehydrated asthmatic patients has frequently proved to be a life-saving measure.[6] It has been our routine practice to have patients drink a solution of dextrose in warm water after an injection of adrenalin for the control of an acute paroxysm. No untoward reaction has been encountered to warrant a change in clinical procedure. In fact, the drinking of a solution of approximately 34 gm. of glucose in water, and even the intravenous administration of a 50 per cent glucose solution with aminophylline, helped alleviate rather than exaggerate severe asthmatic paroxysms in our patient. Tuft's [7] conclusion, that the intravenous use of hypertonic glucose seems to be a valuable adjunct in the treatment of acute severe asthmatic paroxysms, has found universal acceptance. This is significant because of the belief that the problem of corn sensitivity is not limited to certain geographic regions. Therefore, many of the 20 per cent of allergic patients presumably corn sensitive have inevitably received and will continue to receive some form of intravenous glucose therapy at critical stages of their disease. The report of Randolph, Rollins and Walter [8] on allergic reactions following the intravenous injection of corn sugar commands attention. These authors have selected four of several patients shown to be highly corn-sensitive and have administered intravenously 25 c.c. of 5 per cent dextrose solution in each case. Severe constitutional reactions ensued which were clinically similar to those following the ingestion of corn sugar and corn meal. Because of the extensive use of dextrose solutions in treatment, the potential dangers above indicated cannot be minimized, and confirmation is most essential. Nevertheless, one important point must not be overlooked. In the course of desensitization with an extract of an offending allergen, every precaution is taken to prevent accidental intravenous injection with the extract.[9] The results may be dire. Therefore, the intravenous testing of human subjects with a suspected allergenic solution should be undertaken with extreme care, if at all.

As previously noted, three feeding tests with our patient revealed her sensitiveness to corn starch pudding with the production of an asthmatic attack. A

similar reaction followed the application of corn starch granules to the buccal mucosa. Two possible sources of the protein responsible for these positive reactions may be offered in explanation. First, some of the residual protein in corn, about 0.3 per cent on a dry basis, calculated as nitrogen, may be left over on separation of the starch from the gluten water. However, much of this protein is denatured because of the high heat employed in the drying of starch. Second, ordinary commercial starches are not entirely bacteria-free. Contamination resulting from exposure of starch to air and water may occur on the way to the final consumer. The protein residues detectable in corn starch may originate in bacterial cells or enzyme fragments which remain in the starch granules.[10] It is noteworthy, indeed, that Walzer reported one case of sensitiveness to corn starch, whereas Rawling, Sheldon, Halpin and Cazort have not encountered such a case in their study of 10 corn meal-sensitive patients.

Moreover, the consumption of corn oil and of corn syrup (see tables 1 and 2) by our highly corn-sensitive patient was followed by no ill effects whatsoever. According to the earlier concepts, the edible oils derived from oil seeds contained the allergen of the parent material. The work of Bernton, Spies and Stevens [11] failed to uphold this tradition. Their work has been confirmed by Mitchell,[12] Figley [13] and Loveless.[14] It is noteworthy that corn oil as exemplified by this experience follows the pattern of being nonallergenic.

Corn syrup is a product of the controlled partial hydrolysis of corn starch. The bulk of the syrup marketed contains about 34 per cent reducing sugar, calculated as dextrose. The protein content is negligible. The amount of nitrogen in corn syrup commonly listed and accepted by the industry is 0.005 per cent. This residual protein in the syrup is probably more thoroughly denatured than that in starch because of the more severe treatment by heat and chemicals in its manufacture.[10] In 1935, Ratner and Gruehl [15] reported an experimental study in which they showed that corn sugar syrup and crystalline sugar, derived from the hydrolysis of corn starch, were not anaphylactogenic for guinea pigs. They accordingly concluded that these products were unimportant in human allergy. Randolph and Yeager dissent. The loss or denaturing of protein sustained in the processing of some food products may render the final product nonallergenic.

Randolph insists upon certain criteria as evidence of a specific allergic reaction to the ingestion of foods. In addition to symptoms referable to the respiratory and gastrointestinal tracts and skin, he lists the sensation of pulling, drawing tightness in the back of the neck, chilling and goose flesh, tachycardia, perspiration and fatigue as positive reactions in food allergy. Opinion on the important question of diagnostic procedure is divided Those to whom the proposed criteria are not acceptable may test themselves as well as their patients by the "blind-fold technic." The application of the "blind-fold technic" in the diagnosis of food allergy has been fully justified in a study of a case of alleged sensitiveness to cottonseed oil.[16]

It is well to emphasize at this time the criteria, acceptable to Randolph and unacceptable to other investigators, upon which a positive allergic reaction to an ingestion test is based. In the experimental feeding tests conducted with my corn-sensitive patient, an asthmatic attack was the index of a positive reaction. Asthma was the chief complaint of the patient. The respiratory tract constituted the "shock organ." The many minor symptoms, attributed to an allergic

state, are also present in nonallergic conditions and therefore have no decisive diagnostic significance.

Kahn,[17] in a recent discussion of 25 years of experience with food allergy, comments as follows: "Production of symptoms by ingestion of incompatible foods on an empty stomach is of course a requisite from a scientific proof point of view. . . . It is not always possible to secure such confirmation of correctly diagnosed offending foods by dietary resumption on an empty stomach. Patients will not always consent." Another requisite to be added is that deductions be not based on a single observation, positive or negative. This point is well illustrated by Sheldon. He reported that one of his six corn-sensitive patients developed abdominal distress after ingestion of corn starch. When corn starch was mixed with mashed potatoes, concealing its taste, the patient did not have any symptoms. The conclusions to be drawn from our study of a single patient are significant in that they are based upon adequately controlled observations.

A review of the evidence presented herein warrants the following deductions: The provocative ingestion test furnishes a reliable means of diagnosis of food allergy. The suspected food ingested on a fasting stomach must reproduce the allergic symptoms attributed to it. The reliability of the ingestion test is enhanced by excluding or minimizing psychic factors. Sensitiveness to corn meal among the allergic population ranks very low in incidence. Sensitiveness to corn starch is of rare occurrence, presumably among the cases extremely sensitive to corn meal. Sensitiveness to other corn derivatives—corn sugar (dextrose), corn syrup and corn oil—has not been demonstrated by ingestion tests adequately controlled.

The dictum, "The treatment of corn allergy entails the elimination of all sources of corn," is indeed open to question

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